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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/173,463	10/14/1998	MARGARET E. BLACK	240052.429	1873

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/173,463	BLACK, MARGARET E.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-60* is/are pending in the application.

4a) Of the above claim(s) *16-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 October 1998* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-60 are pending in the application. Claims 16-60 have been previously withdrawn from consideration as drawn to a non-elected invention.

2. Claims 1-15 are under consideration in this Office Action.

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 1-15 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants' arguments filed 05/30/2006 have been fully considered but are not persuasive. The examiner respectfully disagrees with applications arguments that the specification supports the locations of the mutations.

Limitations from the specification cannot be read into the claims to further limit the claims. The claims refer to the mutations in the "Q substrate binding domain", 'DRH nucleoside binding site", and mutations at positions that are C- or N-terminal of these domains. However, the claims do not recite the specific amino acid sequence of the mutant *Herpesviridae* thymidine kinase. In view of this, one of skill in the art cannot determine the specific positions where these mutations occur.

Amending the claims to recite the specific amino acid sequence and the specific positions of the mutations may overcome the rejection.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-15 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 are genus claims that are directed toward any isolated nucleic acid molecule of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation alters its substrate specificity in any way. Claims 8-15 are genus claims that are directed toward any isolated nucleic acid molecule of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation results in a thymidine kinase that is capable of phosphorylating any nucleoside analogue including the analogues recited in claim 11.

The scope of the claims includes many nucleic acid molecules with widely differing structural, chemical, and physical characteristics and many mutations that result in any alteration of the substrate specificity of the encoded thymidine kinase or results in the encoded thymidine kinase that is capable of phosphorylating any nucleoside analogue. Furthermore, the genus is highly variable because a significant number of structural differences between genus members exists.

The specification provides general guidance for randomly mutating a polynucleotide of SEQ ID NO: 1 to create mutant polynucloetides having non-wild-type nucleotides for codons corresponding to amino acid residues 112-132 (Q substrate binding domain) of the encoded Herpesviridae thymidine kinase (see Example 10, pp.87-88). The specification states that mutants were assayed for ability to phosphorylate thymidine, acyclovir, and ganciclovir (see p. 88, lines 19-24).

However, the specification does not provide a written description of a specific nucleotide sequence encoding a specific amino acid sequence of mutant *Herpesviridae* thymidine kinases that have mutations in Q substrate binding domain where such mutations result in a thymidine kinase that has any alteration in substrate specificity or ability to phosphorylate any nucleoside analogue. The specification fails to define those structural features that are commonly possessed by members of the claimed genus that distinguish them from other *Herpesviridae* thymidine kinases. Thus, one skilled in the art cannot visualize or recognize the identity of the members of the claimed genus.

In view of the above considerations, one of skill in the art would not recognize that applicants were in possession of the necessary common features or attributes possessed by members of the claimed genus of isolated nucleic acid molecules of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation

in the Q substrate binding domain where said mutation alters the substrate specificity of said thymidine kinase, and the claimed genus of isolated nucleic acid molecules of any nucleotide sequence and structure encoding any *Herpesviridae* thymidine kinase enzyme having any at least one mutation in the Q substrate binding domain where said mutation results in a thymidine kinase that is capable of phosphorylating any nucleoside analogue.

7. Claims 2, 4, 5, 7 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant's arguments filed 05/30/2006 have been fully considered but they are not persuasive.

As stated previously the nature and breadth of claim 2 encompasses any isolated nucleic acid molecule encoding any mutant *Herpesviridae* thymidine kinase having at least three mutations which increases any biological activity; claim 4 encompasses the said isolated nucleic acid molecule further comprising at least one amino acid substitution located 4, 5, 6 amino acid toward the C-terminus from a DRH nucleoside binding site; claim 5 encompasses the said isolated nucleic acid molecule further comprising at least one amino acid substitution located from 1-7 amino acid toward the N-terminus from the DRH nucleoside binding site; and claim 7 encompasses the said isolated nucleic acid molecule where the said enzyme is truncated or contains an in-frame deletion.

While the specification provides general guidance for making for randomly mutating a polynucleotide of SEQ ID NO: 1 to create mutant polynucleotides having non-wild-type nucleotides for codons corresponding to amino acid residues 112-132 (Q substrate binding domain) of the encoded Herpesviridae thymidine kinase (see Example 10, pp.87-88); the specification does not provide specific working examples, guidance, and prediction regarding how to make the claimed polynucleotides without undue experimentation. Thus, an undue amount of experimentation is required to make the claimed invention encompassing making specific nucleotide(s) change(s) (deletion, insertion, substitution, or combinations thereof) in a polynucleotide and screening, searching, and assaying for any polynucleotide that encodes the claimed polynucleotides encoding the mutant thymidine kinase enzymes (full-length or truncated) with the claimed any increase in any "biological activity". . General teachings regarding screening or searching for the invention is not guidance for making the claimed invention.

Thus, such experimentation is well outside the realm of routine experimentation, and without guidance or prediction, the amount of experimentation left to those skilled in the art for making the claimed polynucleotides is undue.

Claim Rejections - 35 U.S.C. § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1, 3, 6, 8-11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Munir et al. in view of Graham et al., Kit et al., Drake et al., Waldman et al., Munch-Petersen et al., Balasubramaniam et al., Brown et al., and Donarian et al. The teachings of each of the references have been stated in the previous Office Actions.

Applicant's arguments filed 05/30/2006 have been fully considered but they are not persuasive. The references of Balasubramaniam et al. and Brown et al. teach that the Q substrate binding domain and the DRH binding domain are important in nucleoside binding and that in order to obtain mutants having the desired properties (i.e. increased enzyme activity or greater substrate/analog/prodrug specificity) this region must be modified. Thus, the teachings of the references provide a motivation to make the claimed invention. One of ordinary skill in the art at the time the invention was made would have used the random mutagenesis method taught by Munir et al. to randomly mutate the codons encoding these important domains in order to obtain and screen for mutants with enhanced properties such as greater substrate, analog, or prodrug specificity and that such mutants having increased activity toward prodrugs such as ganciclovir are expected to be more effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian et al. One of ordinary skill in the art at the time the invention was made would have an expectation of success since recombinant molecular biology techniques for altering nucleic acids are well known and established in the art. Accordingly, claims 1, 3, 6, 8-11 stand rejected.

The disclosure has not been relied upon to reject the claims under 35 U.S.C. 103(a). Instead, the scope and contents of the prior art references were examined, the differences between the prior art and the claims at issue were ascertained, and the claimed invention was found to have been obvious in light of the combined teachings of the references.

10. Claims 12-15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Esandi et al. in view of Munir et al., Graham et al., Kit et al., and Donarian et al. The teachings of each of the references have been stated in the previous Office Action.

Applicant's arguments filed 05/30/2006, have been fully considered but they are not

persuasive. As stated previously, the Donarian et al. reference teaches that the α fetoprotein promoter (a tissue specific promoter) is suitable in the control of prodrug activating or toxic enzymes in the gene therapy of cancer (see **Table 2**, p. 237 and entire publication).

Furthermore, thymidine kinase mutants having increased activity toward prodrugs such as ganciclovir are expected to be more effective in the treatment of cancer when these mutants are used in gene therapy as taught by Donarian et al. (see pp.237-238, section titled *Thymidine kinase*). Thus, the teachings of the references provide a motivation to make the claimed invention. One of ordinary skill in the art at the time the invention was made would have made an expression vector comprising a promoter operably linked to the claimed nucleic acid encoding the claimed *Herpesviridae* thymidine kinase by inserting the mutated DNA encoding mutant thymidine kinase described above in the rejection of claims 1, 3, 6, 8-11 into the expression vector taught by Esandi et al. in order to express thymidine kinase mutants in cancer cells of specific tissue origin.

The disclosure has not been relied upon to reject the claims under 35 U.S.C. 103(a). Instead, the scope and contents of the prior art references were examined, the differences between the prior art and the claims at issue were ascertained, and the claimed invention was found to have been obvious in light of the combined teachings of the references.

Conclusion

11. No claim is allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N

Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

14. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF

TEKCHAND SAIDHA
PRIMARY EXAMINER